

Research Paper

Predictors of Coronary and Carotid Atherosclerosis in Patients with Severe Degenerative Aortic Stenosis

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Abstract

Background. Patients with degenerative aortic stenosis (AS) exhibit elevated prevalence of coronary artery disease (CAD) and internal carotid artery stenosis (ICAS). Our aim was to investigate prevalence of significant CAD and ICAS in relation to demographic and cardiovascular risk profile among patients with severe degenerative AS.

Methods. We studied 145 consecutive patients (77 men and 68 women) aged 49–91 years (median, 76) with severe degenerative AS who underwent coronary angiography and carotid ultrasonography in our tertiary care center. The patients were divided into two groups according to the presence of either significant CAD (n=86) or ICAS (n=22).

Results. The prevalence of significant CAD or ICAS was higher with increasing number of traditional risk factors (hypertension, hypercholesterolemia, diabetes, smoking habit) and decreasing renal function. We found interactions between age and gender in terms of CAD ($p=0.01$) and ICAS ($p=0.06$), which was confirmed by multivariate approach. With the reference to men with a below-median age, the prevalence of CAD or ICAS increased in men aged >76 years (89% vs. 55% and 28% vs. 14%, respectively), whereas the respective percentages were lower in older vs. younger women (48% vs. 54% and 7% vs. 17%).

Conclusions. In severe degenerative AS gender modulates the association of age with coronary and carotid atherosclerosis with its lower prevalence in women aged >76 years compared to their younger counterparts. This may result from a hypothetical “survival bias”, i.e., an excessive risk of death in very elderly women with severe AS and coexisting relevant coronary or carotid atherosclerosis.

Key words: degenerative aortic stenosis; coronary artery disease; carotid atherosclerosis; elderly; gender.

Introduction

Non-rheumatic degenerative aortic stenosis is the most frequent type of acquired valvular heart disease in Europe and North America and its prevalence averages from 2% to 7% in people above 65 years of age [1-4]. Degenerative aortic stenosis and

coronary artery disease (CAD) share many similarities, being chronic, gradually progressive inflammatory disorders. Traditional cardiovascular risk factors are associated with the development of both these conditions [5-7]. According to early clinical studies,

only 40% of patients with severe aortic stenosis have significant CAD and aortic stenosis is absent in the majority of CAD patients, which suggests different pathogenesis of these diseases [8,9]. Additionally, the prevalence of internal carotid artery stenosis (ICAS) $\geq 50\%$ in patients with degenerative aortic stenosis was higher in subjects with coexisting CAD [10].

There is a paucity of reports on determinants of both coronary and carotid atherosclerosis in patients with degenerative aortic stenosis. Our aim was to investigate the prevalence of coronary and internal carotid atherosclerosis in relation to demographic and cardiovascular risk profile among patients with severe degenerative aortic stenosis undergoing diagnostic coronary angiography and carotid ultrasonography in our center.

Patients and Methods

We retrospectively collected data on 145 consecutive patients with severe degenerative aortic stenosis who were admitted to our tertiary care center between January 2003 and October 2012 and underwent elective coronary angiography and carotid ultrasonography during the index hospitalization. The diagnosis of aortic stenosis was confirmed by transthoracic echocardiography. Patients with a non-degenerative etiology of aortic stenosis and subjects with bicuspid or unicuspid aortic valve were excluded from the registry. Coronary angiography was performed as a part of a standard diagnostic procedure on the basis of classical indications: before elective aortic valve replacement and/or due to symptoms suggestive of myocardial ischemia. Demographic and clinical data, including traditional risk factors (arterial hypertension, hypercholesterolemia, diabetes mellitus, smoking) and past medical history (cerebrovascular incident, coronary revascularization) were registered. Biochemical data included serum creatinine, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides measured after an overnight fast during the index hospitalization. Estimated glomerular filtration rate (eGFR) was calculated by the simplified equation developed by the Modification of Diet in Renal Disease (MDRD) Study Group [11]. The ethics committee of our university was notified about the registry and no objection was raised.

All patients underwent transthoracic echocardiography during index hospitalization. We recorded mean and maximal transaortic valve pressure gradients, left ventricular ejection fraction; aortic valve area (AVA) was estimated by means of the continuity equation. Severe aortic stenosis in echocardiography was defined as a mean transaortic gradient >40

mmHg or a calculated AVA <1.0 cm².

Coronary angiography was performed by a standard protocol with a transfemoral or transradial approach and obstructive CAD was defined as the presence of ≥ 1 diameter stenosis of $\geq 50\%$ of at least one major epicardial coronary artery. Carotid arteries were visualized by B-mode imaging using a high-resolution ultrasound device equipped with a 4.0–10.0-MHz vascular transducer (GE Vivid 7; GE Healthcare, Chalfont St. Giles, UK). Cardiovascular risk factors were defined as follows:

- arterial hypertension: systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg in at least 2 measurements or blood pressure requiring medical therapy during index hospitalization or antihypertensive medication prior to admission;
- hypercholesterolemia: fasting total cholesterol >5.2 mmol/l during index hospitalization or diagnosed previously and/or medically treated;
- diabetes mellitus: fasting venous plasma glucose ≥ 7 mmol/l confirmed by repeated testing or casual plasma glucose ≥ 11.1 mmol/l during index hospitalization or diagnosis established before admission;
- smoking: self-reported regular smoking habit.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD) or median and range. The accordance with a normal distribution was confirmed by the Kolmogorov-Smirnov test. Categorical data were shown as numbers and percentages.

The patients were divided into 2 groups according to the prevalence of significant CAD or relevant internal carotid artery stenosis (ICAS). Significant CAD was defined as obstructive CAD (according to the above mentioned criterion) or a history of coronary artery bypass grafting or percutaneous coronary intervention. Relevant ICAS corresponded to a stenosis of $\geq 50\%$ in at least one internal carotid artery. Intergroup differences were calculated by a 2-sided Student's *t* test or the Mann-Whitney's *U* test for continuous data and the χ^2 test or Fisher's exact test for proportions.

Patients' characteristics related to the prevalence of significant CAD or relevant ICAS were identified by logistic regression and odds ratios (OR) with 95% confidence intervals (CI) for predictor variables have been shown. OR represents a multiplicative rise in the odds of a patient having significant CAD or relevant ICAS associated with a change in the explanatory variable. In case of continuous variables, OR is calculated for each one-unit increment in the predictor variable, whereas OR for dichotomous categorical data reflects an increase in the odds of prevalent CAD

or ICAS in the patients exposed to a factor of interest compared to a reference group without this exposure.

As preliminary data analysis indicated that the effect of age on the prevalence of CAD or ICAS could be modified by gender, we created an interaction term that was set to 1 in women with an over-median age (>76 years) being equal to 0 in the remainder study subjects. In order to evaluate the interaction, the interaction term was entered into the regression model in addition to age and gender. Additionally, the interaction was depicted by calculating OR of CAD prevalence for 3 subgroups of subjects created according to gender and age with the reference to women aged >76 years. This latter approach was not applied for ICAS because of a small number of subjects with this condition (n=22).

Independent predictors of the prevalence of relevant CAD or ICAS were identified by multiple logistic regression with backward stepwise variable selection. When building the model, the values of p-to-enter and p-to-remove were set at 0.10 and 0.15, respectively. The goodness-of-fit of the final regression equation was confirmed by the Hosmer-Lemeshow test. A p-value <0.05 was inferred significant.

Results

The registry encompassed data of 145 patients (77 men, 53%) aged 49–91 years (mean 75 ± 9 years). The women enrolled to the registry were significantly older than men (77.4 ± 9.1 vs. 72.2 ± 9.0 years, $p < 0.001$).

Patients' characteristics by the presence of CAD or ICAS have been presented in Table 1 and Table 2, respectively. The occurrence of ICAS and CAD was independent of each other (Tables 1-2). The subjects with significant CAD were more frequently men, exhibited lower eGFR, and tended to be older compared to those without CAD (Table 1). Reduced transaortic valve pressure gradients and decreased left ventricular ejection fraction despite a similar AVA in CAD patients were presumably due to a history of myocardial infarction in the majority of this subgroup (63%) (Table 1). A tendency to lower eGFR was observed in the patients with relevant ICAS with the reference to their counterparts (Table 2). These intergroup differences were reflected by analogous results of univariate logistic regression (Tables 3-4). With regard to traditional risk factors, the occurrence of hypercholesterolemia or diabetes was higher in the subjects with CAD or ICAS, respectively, versus their counterparts, whereas insignificant tendencies were observed for hypertension and diabetes for CAD and hypercholesterolemia for ICAS (Table 1). As the rela-

tions between individual traditional risk factors and CAD or ICAS were unidirectional irrespective of the degree of statistical significance, the number of classical risk factors was entered into logistic regression as one variable, which revealed the association between risk factors clustering and an increased prevalence of CAD (Table 3) and ICAS (Table 4).

The effect of age on the prevalence of CAD and ICAS was different in men and women. With the reference to men with a below-median age (≤ 76 years), the prevalence of CAD increased in men aged over 76 years (by about 60%: 89% vs. 55%), which was not observed in women. Furthermore, the percentage of subjects with CAD was even slightly lower in women aged >76 years compared to women aged ≤ 76 years (48% vs. 54%) (Table 5). A similar pattern was observed for respective proportions of patients with ICAS, being 2-fold higher in men with an over-median age with the reference to those with a below-median age (28 vs. 14%), but over 2-fold lower in older versus younger women (7% vs. 17%) (Table 5).

By logistic regression analysis, the interactions between age and gender were confirmed by a significant effect of the age-gender interaction term on CAD prevalence (OR, 0.58 [95% CI, 0.38–0.88], $p = 0.01$), which was equivalent to a decrease in the odds of prevalent CAD in women with an over-median age. An analogous association was observed for the proportion of ICAS, albeit slightly below the level of statistical significance (OR, 0.63 [0.38–1.02], $p = 0.06$ for the interaction term). With the reference to women aged >76 years, OR of CAD prevalence was significantly increased in men aged >76 years (OR, 3.03 [1.55–5.92], $p = 0.001$), being only slightly higher in younger women (OR, 1.14 [0.69–1.89], $p = 0.61$) and younger men (OR, 1.16 [0.77–1.74], $p = 0.48$).

The strength of these interactions was maintained after multivariate adjustment (CAD: OR, 0.54 [0.35–0.84], $p = 0.006$; ICAS: 0.60 [0.35–1.02], $p = 0.06$ for the age-gender interaction term). In addition to the interaction term, the following covariates were retained in final equations by backward stepwise logistic regression analysis: the number of risk factors (CAD: OR per increment of one, 2.15 [1.33–3.46], $p = 0.002$; ICAS: OR, 2.47 [1.33–4.57], $p = 0.004$), eGFR (CAD: OR per rise of 10 ml/min per 1.73 m^2 , 0.81 [0.70–0.95], $p = 0.007$) and female gender (CAD: OR, 0.71 [0.47–1.06], $p = 0.09$; ICAS: OR, 0.59 [0.33–1.05], $p = 0.07$). The goodness-of-fit of the final regression models for the prevalence of CAD and ICAS was validated ($p = 0.91$ and 0.58, respectively, by the Hosmer-Lemeshow test).

Table 1. Patients' characteristics by the presence of significant CAD.

	No CAD (n=59)	CAD (n=86)	p-value
Demographics			
Age, years	73 ± 10	76 ± 9	0.10
Male sex	26 (44.1%)	53 (61.6%)	0.04
Medical history			
Arterial hypertension	46 (78.0%)	76 (88.4%)	0.09
Hypercholesterolemia	33 (55.9%)	64 (74.4%)	0.02
Diabetes mellitus	17 (28.8%)	35 (40.7%)	0.14
Smoking	5 (8.5%)	10 (11.6%)	0.44
Cerebrovascular event (TIA or stroke)	7 (11.9%)	8 (9.3%)	0.62
Previous CABG	-	11 (12.8%)	
Previous percutaneous coronary intervention	-	38 (44.2%)	
Previous myocardial infarction	-	54 (62.8%)	
Echocardiographic parameters			
Left ventricular EF, % (median [range])	65 [20–84]	56 [20–75]	<0.0001
PG-max., mmHg	104 ± 26	80 ± 25	<0.0001
PG-mean, mmHg	65 ± 19	49 ± 17	<0.0001
AVA, cm ² (median [range])	0.7 [0.3–1.0]	0.7 [0.3–1.0]	0.11
Carotid ultrasound			
Relevant ICAS (≥50%)	7 (11.9%)	15 (17.4%)	0.36
Biochemical parameters			
Total cholesterol, mmol/l	4.5 ± 1.1	4.5 ± 1.1	0.83
LDL-C, mmol/l	2.4 ± 1.1	2.6 ± 0.8	0.56
HDL-C, mmol/l	1.5 ± 0.4	1.3 ± 0.4	0.07
Triglycerides, mmol/l	1.2 ± 0.5	1.4 ± 0.9	0.17
eGFR, ml/min per 1.73 m ²	85.8 ± 26.4	71.9 ± 29.4	0.007

Categorical data are shown as n (%) and continuous data as mean ± SD unless stated otherwise. CAD: coronary artery disease; TIA: transient ischemic attack; CABG: coronary artery bypass grafting; EF: ejection fraction; PG- max.: maximal transaortic valve pressure gradient; PG-mean: mean transaortic valve pressure gradient; AVA: aortic valve area; ICAS: internal carotid artery stenosis; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate.

Table 2. Patients' characteristics by the presence of relevant internal carotid artery stenosis (ICAS).

	No ICAS (n=123)	ICAS (n=22)	p-value
Demographics			
Age, years	75 ± 10	74 ± 8	0.92
Male sex	64 (52.0%)	15 (68.2%)	0.17
Medical history			
Arterial hypertension	102 (82.9%)	20 (90.9%)	0.53
Hypercholesterolemia	79 (64.2%)	18 (81.8%)	0.14
Diabetes mellitus	39 (31.7%)	13 (59.1%)	0.02
Smoking	11 (8.9%)	4 (18.2%)	0.25
Cerebrovascular event (TIA or stroke)	13 (10.6%)	2 (9.1%)	1.00
Previous CABG	9 (7.3%)	2 (9.1%)	0.67
Previous percutaneous coronary intervention	30 (24.4%)	8 (36.4%)	0.29
Echocardiographic parameters			
Left ventricular EF, % (median [range])	60 [20–84]	60 [30–73]	0.71
PG-max., mmHg	90 ± 27	88 ± 33	0.77
PG-mean, mmHg	56 ± 19	51 ± 20	0.24
AVA, cm ² (median [range])	0.7 [0.3–1.0]	0.8 [0.6–1.0]	0.38
Coronary angiography			
Obstructive CAD	71 (57.7%)	15 (68.2%)	0.36
Biochemical parameters			
Total cholesterol, mmol/l	4.5 ± 1.1	4.1 ± 0.9	0.39
LDL-C, mmol/l	2.5 ± 1.0	2.4 ± 0.9	0.74
HDL-C, mmol/l	1.4 ± 0.4	1.2 ± 0.2	0.22
Triglycerides, mmol/l	1.3 ± 0.8	1.2 ± 0.4	0.68
eGFR, ml/min per 1.73 m ²	79.3 ± 27.8	68.1 ± 34.3	0.11

Categorical data are shown as n (%) and continuous data as mean ± SD unless stated otherwise. Abbreviations as in Table 1.

Table 3. Univariate logistic regression analysis of predictors of the prevalence of significant coronary artery disease (CAD) in patients with severe aortic stenosis.

Predictor variable	Odds ratio (OR) of prevalent CAD		
	Wald statistic	Mean OR (95% CI)	p-value
Gender (women vs. men)	4.30	0.70 (0.50–0.98)	0.04
Age (per 10-year increment)	2.75	1.35 (0.95–1.94)	0.10
Number of risk factors (per increment of 1)	7.91	1.76 (1.19–2.61)	0.005
eGFR (per rise of 10 ml/min per 1.73 m ²)	7.21	0.84 (0.73–0.95)	0.007
Aortic valve area (per 0.1 cm ² increment)	3.13	1.20 (0.98–1.47)	0.08

CI: confidence interval; eGFR: estimated glomerular filtration rate.

Table 4. Univariate logistic regression analysis of predictors of the prevalence of relevant internal carotid artery stenosis (ICAS) in patients with severe aortic stenosis.

Predictor variable	Odds ratio (OR) of prevalent ICAS		
	Wald statistic	Mean OR (95% CI)	p-value
Gender (women vs. men)	1.91	0.71 (0.44–1.15)	0.17
Age (per 10-year increment)	0.01	0.98 (0.60–1.58)	0.92
Number of risk factors (per increment of 1)	8.19	2.32 (1.30–4.12)	0.004
eGFR (per rise of 10 ml/min per 1.73 m ²)	2.54	0.87 (0.74–1.03)	0.11
Aortic valve area (per 0.1 cm ² increment)	0.84	1.14 (0.86–1.49)	0.36

Abbreviations as in Table 3.

Table 5. Prevalence of significant CAD and relevant ICAS in relation to age and gender of patients with severe aortic stenosis.

Gender	Age with respect to the median (76 years)	
	≤76 years	>76 years
	Prevalence of significant CAD	
Men (n=79)	28 (55%)	25 (89%)*
Women (n=66)	13 (54%)	20 (48%)
	Prevalence of relevant ICAS	
Men (n=79)	7 (14%)	8 (28%)†
Women (n=66)	4 (17%)	3 (7%)

Data are shown as numbers (%). CAD: coronary artery disease; ICAS: internal carotid artery stenosis.

*p = 0.0003 vs. women >76 years, p = 0.006 vs. women ≤76 years and p = 0.002 vs. men ≤76 years; †p = 0.02 vs. women >76 years by the 2-tailed Fisher's exact test.

Discussion

Our salient finding was a significant effect of gender on the relation between age and the prevalence of angiographic CAD in patients with severe degenerative aortic stenosis. In contrast to men, the prevalence of CAD did not increase in women aged over 76 years compared to women with a below-median age (≤76 years), being even slightly lower. The age-gender interaction in terms of CAD appears counterintuitive because the prevalence of angiographic CAD increases with age in men and women [12]. That this interaction retained statistical significance after adjustment for atherosclerotic risk factors and tended to be present – albeit slightly below the level of statistical significance – for relevant ICAS, suggests an underlying mechanism related to the severity of atherosclerosis, yet other than a different risk profile. A hypothetical explanation for the differential association of CAD and ICAS with age in men and women may be a “survival bias”. According to this concept, women who suffered from both severe

aortic stenosis and relevant coronary or internal carotid atherosclerosis could have been exposed to an excessive risk of death due to coronary or cerebrovascular events, which might have abolished the age-dependent increase in the prevalence of CAD and ICAS in women with aortic stenosis. The limitation of the hypothetical effect to women with aortic stenosis and coexisting CAD or ICAS is consistent with an almost 2-fold higher percentage of women as a whole among our patients with an over-median age, in agreement with a 9-year higher average length of life for women compared to men in our country (80.9 vs. 72.4 years) [13].

We observed a joint contribution of recognized atherosclerotic risk factors to the development of coronary and carotid atherosclerosis in patients with severe degenerative aortic stenosis, which confirms earlier observations. Kablak-Ziembicka et al. reported a higher percentage of diabetes and smoking habit in subjects with degenerative aortic stenosis and concomitant ICAS, however, they also described an in-

dependent effect of coexistent CAD on ICAS, which was not found in the present study [10]. A possible explanation of this inconsistency could be different patients' characteristics because they included 104 subjects aged 63 ± 8 years with moderate-to-severe aortic stenosis [10]. Ortlepp et al. performed an angiographic case-control study in which 523 patients referred for elective diagnostic left heart catheterization because of severe aortic stenosis were compared to controls pair-matched for age, sex and CAD prevalence [14]. In patients with severe aortic stenosis the number of established risk factors predicted the presence of CAD, similar to our data, nevertheless, in the absence of CAD none of the risk factors was significantly more frequent in aortic stenosis compared to those with a normal aortic valve [14]. This finding precipitated the conclusion that classical cardiovascular risk factors could be associated with degenerative aortic stenosis purely on the basis of its association with CAD [14], which appears in disagreement with earlier suggestions that degenerative aortic valve disease was associated with similar factors to atherosclerotic risk factors as demonstrated in 5,201 subjects aged ≥ 65 years enrolled in the Cardiovascular Health Study [6]. Unfortunately, as we analyzed only data of patients with aortic stenosis, our study is not able to clarify this controversy. On the other hand, Goland et al. [15] observed a significantly increased prevalence of hypercholesterolemia in 45 subjects aged 75 ± 10 years with isolated severe degenerative aortic stenosis without angiographic CAD compared to 54 sex- and age-matched controls without aortic stenosis or CAD. Therefore, further investigations are required to identify additional factors which protect against the development of degenerative aortic stenosis despite the presence of atherosclerotic risk factors.

Study limitations

First, this was a retrospective, non-blinded observational study in a relatively low number of subjects and all data were collected from discharge letters and hospital records as source documentation. Due to a retrospective study design, the final dataset might have been incomplete, although we made every effort to ensure that all consecutive patients meeting the inclusion criteria had been included into the registry. Second, the progress in resolution and quality of ultrasound imaging over past 10 years could have influenced the precision of the measurements, nonetheless, cardiac and carotid ultrasound were performed by experienced sonographers. Third, eGFR was calculated from the highest level of serum creatinine measured during the index hospitalization, nevertheless, time points of blood sampling were not standardized. Finally, the evaluation of coronary and

carotid stenoses was based mostly on visual assessment and a quantitative analysis was not performed by an independent core laboratory.

Abbreviations

AS: aortic stenosis; AVA: aortic valve area; CAD: coronary artery disease; CABG: coronary artery bypass grafting; CI: confidence interval; EF: ejection fraction; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; ICAS: internal carotid artery stenosis; LDL-C: low-density lipoprotein cholesterol; OR: odds ratio; PG-max.: maximal transaortic valve pressure gradient; PG-mean: mean transaortic valve pressure gradient; SD: standard deviation; TIA: transient ischemic attack.

Competing Interests

The authors have declared that no competing interest exists.

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